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# Correspondence

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## Volume of parahippocampal gyrus and hippocampus in schizophrenia

**Sir:** Razi *et al* (1999) report a reduction in the volume of the parahippocampal gyrus and the hippocampus in patients with chronic schizophrenia. They also show an interaction with gender such that only females with chronic illness have smaller hippocampi. However, there are a number of problems with their study that should be addressed.

First, the authors have overlooked important literature in this area. There have been recent studies that are relevant to their findings, including a meta-analysis (Nelson *et al*, 1998) and a large-scale review (Lawrie & Abukmeil, 1998). Both of these articles conclude that schizophrenia is associated with a bilateral volumetric reduction of the hippocampus and amygdala. The patient populations reviewed in these papers were predominantly male and chronically ill, which contrasts with the data reported by Razi *et al* (1999). Further, two recent articles support the findings of these reviews. In the study by Hirayasu *et al* (1998), smaller volume of left posterior amygdala–hippocampal complex was identified in patients with first-episode schizophrenia/schizophreniform psychosis. In our study (Velakoulis *et al*, 1999), using a reliable method to trace the hippocampus only, smaller left hippocampal volumes were found in patients with first-episode psychosis, as well as in patients with chronic schizophrenia, in comparison with a large group of 140 normal controls. We have recently found that these changes were specific to males with schizophrenia; females did not differ from normal controls.

Second, in the study by Razi *et al* (1999) there may be inadequate power to detect volumetric differences in the first-episode psychosis patients (there were only seven males and six females in their first-episode sample). Our study (Velakoulis *et al*, 1999) suggested there were reduced hippocampal volumes in first-episode psychosis regardless of a diagnosis of affective psychosis or schizophrenia/schizophreniform psychosis.

Third, methodologies are available to reliably segment the hippocampus from amygdala using manual tracing (Cook *et al*, 1992). The definition of hippocampus and amygdala by Razi *et al* (1999) relies on external landmarks that may be subject to artefact such as the orientation of the brain (there is no indication that realignment of brains occurred prior to tracing). Tracing the hippocampus and amygdala as a single structure unnecessarily confounds statistical analysis. In addition, the mechanism of obtaining whole-brain volume is suboptimal, since a volume measurement was obtained only on slices containing the regions of interest. No rationale was offered for this procedure, nor an assurance of its validity. Also, only intra-rater reliability measures are reported, and then not specifically for each structure.

Finally, Razi *et al* (1999) suggest that the hippocampal volume reduction may be an artefact of ventricular enlargement. The implication is that there may be compression of the hippocampus by an enlarged ventricle, which would imply raised cerebrospinal fluid pressure. To our knowledge, there is no evidence of ventricular obstruction or hydrocephalus in schizophrenia. Interestingly, Razi *et al* (1999) note that they could not perform measurements on the temporal horn owing to its small size.

In summary, there are a number of methodological issues that may explain the difference between this study and a large body of literature that has identified reduced hippocampal volumes in schizophrenia.

**Cook, M. J., Fish, D., Shorvon, S., *et al* (1992)** Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. *Brain*, **115**, 1001–1015.

**Hirayasu, Y., Shenton, M. E., Salisbury, D. F., *et al* (1998)** Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. *American Journal of Psychiatry*, **155**, 1384–1391.

**Lawrie, S. M. & Abukmeil, S. S. (1998)** Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *British Journal of Psychiatry*, **172**, 110–120.

**Nelson, M. D., Saykin, A. J., Flashman, L. A., *et al* (1998)** Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: A meta-analytic study. *Archives of General Psychiatry*, **55**, 433–440.

**Razi, K., Greene, K. P., Sakuma, M., *et al* (1999)** Reduction of the parahippocampal gyrus and the hippocampus in patients with chronic schizophrenia. *British Journal of Psychiatry*, **174**, 512–519.

**Velakoulis, D., Pantelis, C., McGorry, P. D., *et al* (1999)** Hippocampal volume in first-episode psychoses and chronic schizophrenia: A high-resolution magnetic resonance imaging study. *Archives of General Psychiatry*, **56**, 133–140.

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**Author's reply:** Dr Wood *et al* suggest that the significance of our results is limited by several problems. In our report (Razi *et al*, 1999) we presented data from precise measurements of the hippocampus and parahippocampal gyrus on thinly sliced magnetic resonance imaging (MRI) scans. These show reduced volumes of both structures in individuals with schizophrenia, but only in patients with chronic schizophrenia and not in those with a recent onset of illness. We interpreted this finding to be consistent with the growing evidence that the brain continues to change after the onset of illness along with the development of chronicity (DeLisi, 1997; DeLisi *et al*, 1997; Woods, 1998; DeLisi, 1999). We also speculated that the reports in the literature of reduced volumes of the hippocampus on MRI may be due to the masking of hippocampal boundaries by subtle enlargement of the temporal horns of the lateral ventricles, rather than loss of hippocampal volume itself (i.e. an artefact of magnetic resonance images, not hydrocephalus as Wood *et al* thought we were implying). The latter was based on our review of the literature (Table 1 in Razi *et al*, 1999) and that of Dwork (1997) showing inconsistencies between findings of reduced hippocampus on MRI and a failure to replicate this finding in the majority of post-mortem studies in which the actual boundaries of hippocampus can

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be obtained. Since the publication of our report, a post-mortem study by Crow and colleagues has been completed showing no significant change in total and sub-field volumes and neuronal density within the hippocampus of patients with schizophrenia (T. J. Crow, personal communication, 1999). Since lateral ventricular size may be expanding over time and cortical volume decreasing in patients with chronic schizophrenia (DeLisi, 1999), one has to account for why post-mortem studies of patients who have been ill for several years (at the 'end-stage' of illness) find little evidence for pathology of the hippocampus.

The first point that Wood *et al* raise is that we appeared to overlook two recent reviews in the literature that conclude that the hippocampus is reduced in schizophrenia bilaterally. Neither of these reviews, however, deals with the inconsistencies I raise above (they review MRI, but not post-mortem studies), or with the issue of measurement variability. The anatomical delineation of the hippocampus as it is visualised on MRI scans is difficult. Separation from the boundary of the parahippocampal gyrus may vary between observers, and the anterior and posterior boundaries are frequently difficult to define. In general, the thicker the MRI slice, the more inaccurate the measurements are likely to be. In fact, interrater reliability for measurements of these medial limbic structures is usually reported to be low. The temporal horns of the lateral ventricles are even more difficult to measure accurately, because of their irregular shape; in controls they are small and irregularly visualised. For these and the other reasons listed above, we conclude from our own review of the literature (in Table 1 of Razi *et al*, 1999) that the findings in the medial termporal lobes of patients with schizophrenia are inconsistent. Wood *et al* mention an additional problem of how one chooses to separate amygdala from hippocampus. However, this seems irrelevant to their argument since both reviews they cite conclude that both the amygdala and the hippocampus are reduced.

Wood *et al*, raise a second issue that suggests a lack of validity of our failure to find evidence for medial temporal lobe pathology in first-episode patients because it is present in other recent studies of first-episode schizophrenia. Although the number of subjects scanned at the first episode in our own study is small, this is unlikely to account for the discrepancy. Positive studies such as Hirayasu *et al* (1998) cited by Wood *et al* also studied a small cohort, particularly when considering that 12 of their 17 'first-episode' cases were ill at least six months prior to the initial hospitalisation and an another two were not scanned until a follow-up evaluation at 15 and 22 months. Thus, perhaps what accounts for the discrepancy is a problem with the term 'first-episode'. One assumes that by studying patients at the time of their first hospitalisation (usually also their first episode), they are being studied at the onset of the disorder. However, brain structural change and subtle behavioural symptoms could have been occurring for several years prior to the identification of the first episode (DeLisi, 1992). Thus, the timing of the development and ability to detect brain changes is likely to vary across small samples of patients.

Finally, the question was raised as to why measurement of total brain volume was obtained only on slices in which the medial temporal lobe structures were measured. This method was thought to be valid since the medial temporal lobe appears in only a small portion of the total number of slices covering the entire brain and it is likely that medial temporal lobe volumes are not linearly correlated with total brain volume. We also wanted to determine whether reduced total brain volume specifically within the region where the medial temporal lobe appears could account for our results. Thus, we thought the use of this partial volume would be a valid way to control for brain size in analyses. However, whether these measurements should be controlled for brain size at all, given the studies showing overall hemispheric volume reduction in schizophrenia, is a more important issue. In Razi *et al* (1999) the volumes of medial temporal lobe structures were compared with and without brain size as a covariate and the findings did not differ. In addition, a subsequent analysis was performed on the same data substituting the height of each individual for brain volume to eliminate the confound of overall brain volume reduction in schizophrenia, yet still controlling for the size of the individual. There were no differences in height among diagnostic subgroups and all previously significant results remained the same. Both hippocampus and parahippocampus were reduced in patients compared with controls ($F=6.7$, $P<0.002$ and $F=7.6$, $P<0.001$). The *post hoc* analyses show differences only in chronic, not in first-episode patients, and are as reported in Razi *et al* (1999).

I therefore conclude that the objections of Wood *et al* in no way negate the possibility that any observed reduction of the hippocampus seen on MRI in patients with schizophrenia could be due to a primary enlargement of lateral ventricles (the temporal horn of which interferes with measurements of hippocampus), and that this expansion of ventricular space continues sporadically through the chronic course of schizophrenia, to a greater extent on the left than the right and possibly in those with a poor course.

**DeLisi, L. E. (1992)** The significance of age of onset for schizophrenia. *Schizophrenia Bulletin*, **18**, 209–215.

**— (1997)** Is schizophrenia a lifetime disorder of brain plasticity, growth and aging? *Schizophrenia Research*, **23**, 119–129.

**— (1999)** Regional brain volume change over the life-time course of schizophrenia. *Journal of Psychiatric Research*, in press.

**—, Sajkuma, M., Tew, W., *et al* (1997)** Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Research*, **74**, 129–140.

**Dwork, A. J. (1997)** Postmortem studies of the hippocampal formation in schizophrenia. *Schizophrenia Bulletin*, **23**, 385–402.

**Hirayasu, Y., Shenton, M. E., Salisbury, D. F., *et al* (1998)** Lower left temporal lobe MRI volumes in patients with first-episode schizophrenia compared with psychotic patients with first-episode affective disorder and normal subjects. *American Journal of Psychiatry*, **155**, 1384–1391.

**Razi, K., Greene, K. P., Sakuma, M., *et al* (1999)** Reduction of the parahippocampal gyrus and the hippocampus in patients with chronic schizophrenia. *British Journal of Psychiatry*, **174**, 512–519.

**Woods, B. T. (1998)** Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. *American Journal of Psychiatry*, **155**, 1661–1670.

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## Post-abortion mania

**Sir:** It has been suggested that the oestrogen decrease occurring after delivery plays an aetiological role in puerperal psychoses (Deuchar & Brockington, 1998). Acute psychosis following abortion is a very rare disorder (incidence 0–3/1000 induced abortions) (Brewer, 1977) and has been rarely documented. We describe the case of a woman who presented with psychotic mania following abortion.

Mrs A. experienced puerperal mania with psychotic features when she was 19,